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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
03/21/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,836	GUGLIELMOTTI ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 1/3/2011.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 6-12,14-23 and 25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6-12,14-23 and 25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The office acknowledges the receipt of the amendments, remarks and arguments received on 1/3/2011. Claims 1-5, 13, 24 have been cancelled. Claims 6, 16 and 17 have been amended. Claim 25 has been added new. Claims 6-12, 14-23, 25 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' amendments and addition of new claim necessitated the modified and the new rejection presented in this action. Applicants' arguments regarding the 103 rejections have been fully considered and found not to be persuasive. The arguments are addressed in the Response to Arguments section below. The action is made Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have claimed in claim 25 "the method of claim 6, wherein said neuropathic pain is not associated with non-neuropathic pain". Applicants in the response (dated,1/3/2011) state that "Claim 25 which indicates that neuropathic pain is not associated with other types of chronic pain, finds support on

page 2, lines 1 and 9. There is no support for the statement that "wherein said neuropathic pain is not associated with non-neuropathic pain" in line 1 or line 9 of the specification and it is new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 6-12, 14-23, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US 2004/0038874, effective filing date Aug 22 2002) in view of Gaster et al (EP 0630376).

Omoigui's teachings disclose a method for treating persistent pain by inhibiting mediators of inflammation including serotonin. (Omoigui, Abstract). Omoigui teaches that "antagonism of inflammation and the inflammatory response will relieve pain of every origin, type and character." (para [0004]). Omoigui further teaches that "the hallmarks of neuropathic pain are chronic allodynia and hyperalgesia." (para [0072]).

Embodiments of Omoigui's method includes treating "neuropathic pain syndrome including neuralgia or nerve pain, carpal tunnel syndrome, post herpetic neuralgia" (p 11, claim 12), and administering a serotonin receptor antagonist (p 13, claim 80). The reference further teaches that serotonin receptor antagonist is administered intramuscularly, intravenously, subcutaneously, orally or rectally (p 13, claim 84).

The reference Omoigui do not teach the claimed compounds in a method of treating neuropathic pain.

Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT4, serotonin receptor antagonists (p1 lines 6-8) and further teaches a method of treatment of irritable bowel syndrome, migraine etc in mammals (p6, lines 42-43) comprising administering these compounds.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used the compounds of formula I in the treatment of neuropathic pain based on the teachings of Omoigui and Gaster. Omoigui explicitly teaches treating neuropathic pain with a serotonin receptor antagonist (p11, claim 12, p 13, claim 80). Gaster teaches the compounds of formula I to be 5-HT4, serotonin receptor 4 antagonists. It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered Gaster's serotonin receptor 4-antagonist compounds to treat neuropathic pain in the method of Omoigui in expectation of similar or better therapeutic benefits. A person of ordinary skill in the art at the time of the invention would have been motivated in using Gaster's serotonin receptor antagonist compounds for Omoigui's serotonin receptor antagonist in a method of treating neuropathic with a

reasonable expectation of success because Omoigui explicitly teaches treating neuropathic pain with a serotonin receptor antagonist. Omoigui teaches that the hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. Omoigui teaches neuropathic pain can be treated in general with all types of serotonin receptor antagonists which includes serotonin type 4 antagonists. Hence from Omoigui's teachings it would have been obvious to a person of ordinary skill in the art to choose a serotonin receptor antagonist, such as 5HT-4 antagonist such as Gaster's compounds in a method of treating neuropathic pain or allodynia, a clinical finding in neuropathic pain.

It would have been obvious to a person of ordinary skill in the art at the time of the invention from the teachings of Omoigui that allodynia and hyperalgesia are hallmarks of neuropathic pain. Hence a subject suffering from neuropathic pain as claimed (claims 16, 17) would have allodynia and/or hyperalgesia as frequent symptoms of the neuropathic pain disease.

It would have been obvious to a person of ordinary skill in the art, at the time of invention to have used Gaster's compound in a method of treatment to a subject who has neuropathic pain, irrespective of whether the pain is induced either as a result of cancer or diabetes or otherwise (claims 18, 19) because Omoigui teaches that persistent pain disorders including neuropathic pain can be treated by serotonin receptor antagonist. Neuropathic pain is a symptom associated with many diseases and the cause of the pain or the diseases associated with the pain is irrelevant if neuropathic pain can be treated by administration of a drug. Thus as the prior art teaches treating

neuropathic pain, pain associated with any disorder, including diabetes or cancer will be treatable by administration of Gaster's serotonin receptor antagonist compounds. Omoigui teaches a method for treating persistent pain disorders by inhibiting the biochemical mediators of inflammation in a subject comprising administering to said subject a therapeutically effective dosage of inhibitor such as serotonin receptor antagonist (claims 1, 80). The reference does not teach addition of any other active ingredient. Accordingly, administration of a serotonin receptor antagonist such as compound of formula I of Gaster addresses the limitation of administration of a compound of formula I as the active ingredient in claim 1. With respect to claims 16 and 17 if the neuropathic pain is treated by administration of compounds of formula I the clinical allodynia or hyperalgesia is treated regardless of the source of the symptom.

Response to Arguments

(1) 103(a) rejection under 35 U.S.C. 103(a) as being unpatentable over Omoigui, et al., U.S. 2004/0038874, in view of Gaster et al., EP 0630376.

Applicants' argue that these documents do not render the claimed invention obvious because they do not suggest or provide a reasonable expectation of success for treating neuropathic pain (associated with damaged nerve tissue) using a compound of formula (I).

In response, Omoigui et al. in general teaches a method for treating persistent pain disorders by inhibiting the biochemical mediators of inflammation in a subject comprising administering to said subject a therapeutically effective dosage of inhibitor including serotonin receptor antagonist (claims 1 and 80). The reference teaches

treating persistent pain disorder such as migraine, neuropathic pain syndrome including neuralgia or nerve pain, carpal tunnel syndrome, post herpetic neuralgia, phantom limb pain, vulvodynia by inhibiting the biochemical mediators of inflammation. Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT4, serotonin receptor antagonists. Gaster in para 0040 teaches that administration of a 5-HT4 antagonist is of potential benefit in relieving a migraine attack. Omoigui teaches that by inhibiting the biochemical mediators of inflammation persistent pain disorder which includes both migraine and neuropathic pain syndrome can be treated. In addition the reference teaches serotonin receptor antagonist as one of the inhibitors. Gaster provides a method of treatment of migraine with 5-HT4, serotonin receptor antagonists (compounds of formula I). Hence it would have been obvious to a person of ordinary skill in the art at the time of the invention to have tried using the same compounds in treating neuropathic pain syndrome from the teachings of Gaster and Omoigui. In addition, as stated by Applicants (in the response in p 10) Gaster clearly discloses the potential therapeutic indications for 5-HT4 receptor antagonists and discloses four main categories of disorders: gastrointestinal, CNS, cardiovascular and urinary bladder (para 0034, Gaster). Neuropathic pain is pain caused by lesion or dysfunction of the nervous system and one of the etiologies of neuropathic pain is central nervous system disorder. Accordingly it would have been obvious from Gaster's teachings to use a compound of formula I, a serotonin receptor 4 antagonist in treating pain including neuropathic pain.

Applicants argue that claims 17 and 18 further characterize allodynia and hyperalgesia associated with nerve damage and new claim 25 further refers to

treatment of neuropathic pain that is not associated with non-neuropathic chronic pain, such as migraine. Thus, Gaster does not disclose or suggest use of these compounds for treating neuropathic pain associated with damaged nerves.

In response, Gaster clearly discloses the potential therapeutic indications for 5-HT4 receptor antagonists and discloses four main categories of disorders: gastrointestinal, CNS, cardiovascular and urinary bladder (para 0034, Gaster). Neuropathic pain is pain caused by lesion or dysfunction of the nervous system or neuropathic pain is defined as pain resulting from lesions in the CNS and hence treating a CNS disorder also treats neuropathic pain associated with that. One of the etiologies of neuropathic pain is central nervous system disorder. Accordingly it would have been obvious from Gaster's teachings to use a compound of formula I, a serotonin receptor 4 antagonist in treating pain including neuropathic pain. Also, if the neuropathic pain is treated by administration of compounds of formula I the clinical allodynia or hyperalgesia is treated regardless of the source of the symptom.

Applicants argue that the number of serotonin receptors identified up to now amounts to almost twenty and Wikipedia lists a number of serotonin receptor antagonists and none of these antagonists was ever used or proposed for treating neuropathic pain and the art at the time of invention did not disclose or suggest using a serotonin receptor antagonist, and even less a 5-HT4 serotonin receptor antagonist, to treat pain or even less neuropathic pain, which was then known to be a specific and peculiar type of pain associated with nerve damage that results in the sensation of pain and which differs from regular nociceptive pain. Applicants" argue that there is no

suggestion in the prior art to employ serotonin receptor antagonists, especially 5-HT4 receptor antagonists for treatment of neuropathic pain

In response, prior art Omoigui teaches a method of treating persistent pain disorders that includes migraine, neuropathic pain syndrome including neuralgia or nerve pain, carpal tunnel syndrome, post herpetic neuralgia, phantom limb pain, vulvodynia by inhibiting the biochemical mediators of inflammation such as serotonin receptor antagonist. Gaster teaches that administration of a 5-HT4 antagonist is of potential benefit in relieving a migraine attack and further discloses the potential therapeutic indications for 5-HT4 receptor antagonists in CNS disorders. Accordingly, the prior art provides suggestion to use serotonin receptor antagonists in treating pain including neuropathic pain. A person of ordinary skill in the art would have found it obvious to use compounds of formula I (serotonin receptor 4 antagonists) in treating neuropathic pain because Gaster teaches the making of such compounds and their use in treating migraine and CNS disorders and neuropathic pain is defined as pain resulting from lesions in the CNS and one of the etiologies of neuropathic pain is central nervous system disorder.

Conclusion

No claims are allowed.

Applicants' amendments necessitated the new rejection and the modified rejection in this action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627